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Non-Cancer Dose-Response Assessments Within the EPA (Environmental Protection Agency): A Foundation for Selecting a Dose-Response Assessment Method to Assess Section 112 Pollutants Based on Non-Cancer Effects

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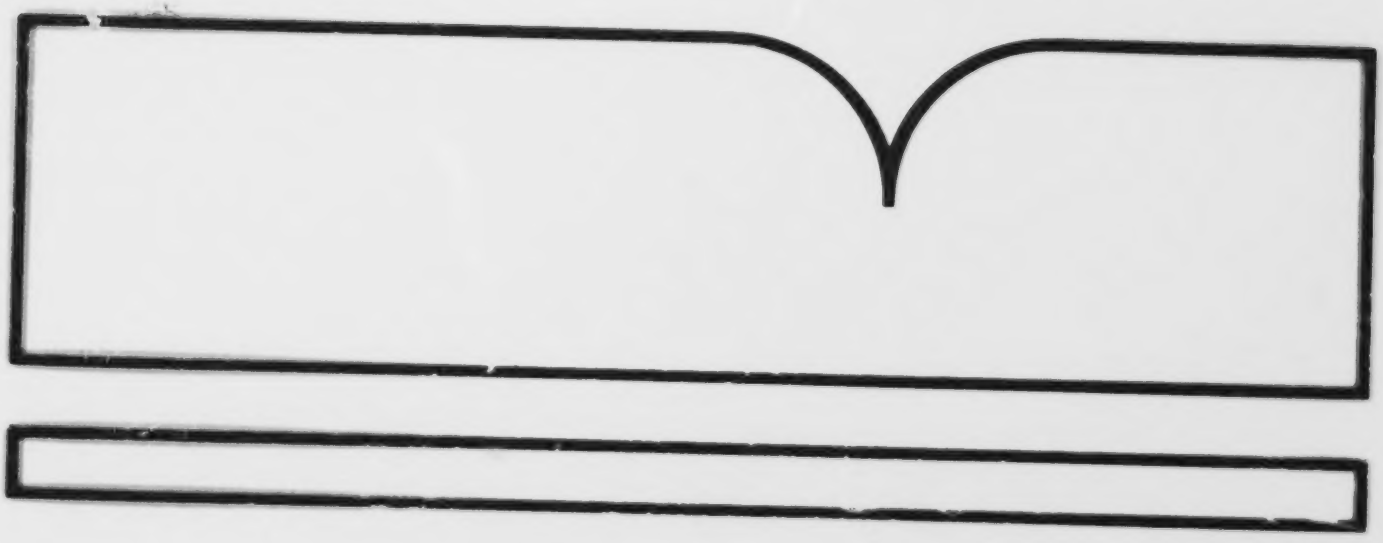

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This report is part of the National Network for Environmental Management Studies conducted under the auspices of the Office of Cooperative Environmental management - U. S. Environmental Protection Agency. Regulations concerning hazardous pollutants within the EPA's Office of Air and Radiation have historically focused on chronic continuous exposure, with cancer as the chief health endpoint of concern. Exposures to these hazardous substances are averaged over an annual period, allowing for exposure levels to fluctuate over short periods of time (e.g. episodic releases of a plume through a pressure relief valve would contribute to such fluctuations). There is concern that significant non-cancer risks may result from these episodic exposures.

These concerns as well as concerns over accidental releases (e. g. Bhopal) have focused attention on non-cancerous effects in the risk assessment process within EPA. This attention has raised questions regarding how risks associated with these effects can and should be assessed, and what are the policy considerations in making such decisions? Specifically, the Office of Air and Radiation is considering non-cancer effects in developing regulations under its NESHAP program. This report intends to provide a foundation for a decision on how risks from non-cancer effects should be assessed in developing regulations under the NESHAP program. This foundation will be built by focusing on trends in current non-cancer risk assessment practices across program offices within the Agency, and (to the extent such information is available) the conditions which have driven these trends. This report will focus on the dose-response evaluation (a step in the risk assessment process).

The sources of information relied on for this study include reports and various other EPA documents , as well as interviews of personnel in the EPA Office of Water, Office of Solid Waste, Office of Drinking Water, Office of Toxic Substances, Office of Air and Radiation, and the Office of Pesticide Programs.

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OFFICE OF POLICY ANALYSIS AND REVIEW

NON-CANCER DOSE-RESPONSE ASSESSMENTS WITHIN THE EPA: A FOUNDATION FOR SELECTING A DOSE-RESPONSE ASSESSMENT METHOD TO ASSESS SECTION 112 POLLUTANTS BASED ON NON-CANCER EFFECTS

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1988 NNEPS PROJECT REPORT

Disclaimer

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STATEMENT OF THE PROBLEM

Regulations concerning hazardous pollutants within the Office of Air and Radiation have historically focused on chronic continuous exposure, with cancer as the chief health endpoint of concern. Exposures to these substances are averaged over an annual period, allowing for exposure levels to fluctuate over short periods of time (e.g. episodic releases of a plume through a pressure relief valve would contribute to such fluctuations). There is concern that significant non-cancer risks may result from these episodic exposures.

These concerns as well as concerns over accidental releases (e.g. Bhopal) have focused attention on non-cancerous effects in the risk assessment process within EPA. This attention has raised questions regarding: how risks associated with these effects can and should be assessed, and what are the policy considerations in making such decisions? Specifically, the Office of Air and Radiation is considering non-cancer effects in developing regulations under its NESHAP program. This report intends to provide a foundation for a decision on how risks from non-cancer effects should be assessed in developing regulations under the NESHAP program. This foundation will be built by focusing on trends in current non-cancer risk assessment practices across program offices within the Agency, and (to the extent such information is available) the conditions which have driven these trends. Specifically, this report will focus on the dose-response

evaluation (a step in the risk assessment process).[1]

The sources of information relied on for this study include reports and other various EPA documents, as well as interviews of personnel in the EPA Office of Water, Office of Solid Waste, Office of Drinking Water, Office of Toxic Substances, Office of Air and Radiation, and the Office of Pesticide Programs.

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[1] Other steps of the risk assessment process are important to the outcome of the assessment of risks from non-cancerous effects; however, time and attention limitations restrict the focus of this report. The dose-response assessment will receive primary focus, because it represents the principal point of departure of non-cancer risk assessments from cancerous risk assessments. Elements of the other risk assessment steps will be mentioned in this paper where relevant.

INTRODUCTION

The primary elements of human health risk from chemical agents include: the likelihood that a substance will produce an effect (identification of a hazard); the relationship of exposure level to incidence in the population (relationship of dose to response); and the extent of possible human exposure to the substance (exposure estimate). The National Research Council has used these elements to constitute a framework for the risk assessment process (NRC, 1983). The EPA has adopted this framework to guide Agency risk assessments. As a result, this framework is assumed in this examination of how the program offices perform their risk assessments.

As indicated above, this report focuses on the dose-response assessment. The goal of the dose-response evaluation is to determine how much of a hazard exists from a substance at varying doses. The measure of hazard is in terms of the percentage of the population expected to incur the disease at a given dose. To arrive at such population percentages, cancer dose-response assessments extrapolate from experimental animal response data to predicted human responses (the predicted response is expressed as a probability, i.e. 10^{-6}). However, a difference in fundamental assumptions (i.e. threshold and non-threshold effect), and a lack of knowledge regarding the operation of non-cancer effect mechanisms, has caused difficulties in applying the type of extrapolation performed in the cancer assessment to the non-cancer

assessment (see EPA, 1986; EPA, 1988c; EPA, 1988e).

The EPA generally assumes that for non-cancer effects a threshold exists below which no effect occurs. This concept of a threshold effect is based on the theory that an organism can tolerate certain doses of a toxic substance before an adverse effect is manifested, due to repair and detoxification mechanisms:

> "...organic homeostatic, compensating, and adaptive mechanisms exist that must be overcome before a toxic endpoint is manifested. For example, there could be a large number of cells performing the same or similar function whose population must be compromised before a toxic effect is seen." (EPA, 1988h).

However, it is not always clear when the toxic or adverse effect has become manifest. It is argued that certain situations identifying a threshold effect is largely a subjective decision. For example, one of the effects from acute ozone exposure is reduced pulmonary function. The Office of Air and Radiation measured such reduced function in terms of breathing capacity. Ten percent and twenty percent reductions in breathing capacity were noted at two different exposure levels. The question faced by the Air Office is: when should such reductions in capacity be considered adverse? As a result, non-cancer risk assessments focus on the relationship of the <u>severity</u> of response with dose, as well as the relationship of incidence with dose. In contrast, the no-threshold assumption does not recognize intermediate endpoints (i.e. the severity of the cancer response is assumed constant).

This problem of defining adverse effects is the cause of much conflict among Agency toxicologists.

The concept of a threshold is important to regulatory considerations since it implies a safe level of exposure. However, the ability to scientifically identify population thresholds for most substances is problematic.[2] Nevertheless, two alternative dose-response assessment methods have been used in risk assessments for non-cancer health endpoints. Each of these techniques treat the concept of a population threshold differently. A general description of each of these methods is given below, followed by examples of applications by EPA program offices.

I. ALTERNATIVE DOSE-RESPONSE ASSESSMENT METHODS[3]

The two approaches within EPA that have been used to evaluate the dose-response relationship in the context of non-cancer effects are: the Rfd approach and modelling.

A) The Reference Dose (Rfd) Approach

The Rfd approach has been the traditional and most widely used means of performing dose-response assessments within the EPA. This method has been in use in regulatory

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[2] Cote (EPA, 1987g) has cited a number of the problems associated with identifying a population threshold.

[3] This section borrows heavily from: EPA, 1987g.

contexts for over twenty years, and was first introduced in the context of determining toxic properties of food additives (EPA, 1985). The EPA, the FDA, the World Health Organization and various committees of the National Academy of Sciences use the Rfd procedure.

The Rfd involves the identification of an empirically derived "no observed adverse effect level" (NOAEL) or a "lowest observed adverse effect level" (LOAEL) along with the application of an uncertainty factor to arrive at the final Rfd value. The Rfd approach assumes a threshold response, and doses at the Rfd are considered to have little health risk.[4] The EPA notes that:

> "The ADI [Rfd] is commonly defined as the amount of a chemical to which a person can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect." (EPA, 1988h).

Uncertainty is factored into the Rfd calculation by dividing the NOAEL or LOAEL by some power of ten (e.g.

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[4] The term Rfd was introduced in the past few years to replace "Acceptable Daily Intake" (ADI). The change in terminology did not appear to correspond to any substantive changes in the procedures followed to calculate the number. "Rfd" was considered to have fewer implications for safety than "ADI", which appears to have been one of the chief reasons for the change in terminology. The EPA does not consider the Rfd/ADI value risk free: "The ADI represents an acceptable, low level of risk but not a guarantee of safety. Conversely, there may be a range of exposures well above the ADI, perhaps including the experimental NOEL itself, that bears no risk to humans" (EPA (1987d).

Despite efforts to obtain uniformity in the terminology, "ADI" remains in use. As a result, the terms Rfd and ADI may be used interchangeably in this report.

the greater the uncertainty the greater the divisor by "orders of magnitude"). The choice of the uncertainty factor is based on an evaluation of the available data. Guidelines regarding the application of uncertainty factors in the Rfd calculation are discussed in greater detail below.

1) Application of Uncertainty Factors

General EPA guidelines regarding the application of uncertainty factors to the Rfd calculation identify five general areas of uncertainty which are possible when extrapolating from various types of data to arrive at the Rfd (EPA, 1988h). The guidelines also provide an additional modifying factor to essentially fine tune the uncertainty assessment. The modifying factor allows risks assessors to exercise professional judgment and modify the uncertainty factor by a factor from one to ten. The size of the modifying factor is determined by data considerations not covered by the standard guidelines (i.e. overall completeness of the data base, number of animals tested, etc.).

Instead of dividing the NOAEL by uncertainty factors to arrive at the Rfd, an alternative approach is used involving the division of the NOAEL by an exposure quantity to arrive at a "margin of exposure".[5] The margin of

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[5] The "margin of exposure" is also referred to as the "margin of safety".

exposure is considered conceptually similar to the uncertainty factor. The primary difference is that the two are computed differently and are used in different regulatory situations.

EPA describes the difference between the two approaches as follows:

> "The uncertainty factor approach results in a calculated exposure level believed to be unlikely to cause any toxic developmental response in humans, while the margin of exposure approach derives a ratio of the NOAEL to the estimated human exposure level. The adequacy of the margin of exposure is then considered based on weight of evidence, including the nature and quality of the hazard and exposure data, the number of species affected, and other factors such as benefits of the agent" (EPA, 1986).

The choice of the uncertainty factor approach or the margin of safety approach has been considered dependant upon many factors, "including the statute involved, the situation being addressed, the data based used, and the needs of the decision-maker" (EPA, 1986). The EPA currently considers the MOE as part of the risk characterization process (EPA, 1988c).

2) Rfd Workgroup

In 1985 meetings between representatives of the Office of Pesticides, Office of Drinking Water, and the Office of Research and Development took place to develop consistency in the ADI process within the Agency. An inter-office workgroup was eventually formed (Rfd workgroup)

which now "verifies" Rfd values for use on an Agency wide basis. All program offices are represented at the workgroup meetings, and are required to rely on the workgroup's numbers when utilizing Rfd values (Thomas, 1987).

At the time of the first workgroup meetings the program offices had developed ADIs for approximately 400 substances, and approximately 10% were in conflict . There are currently 600 to 700 ADIs in existence; approximately 400 of these numbers have been verified. The results of the workgroup's verification process are incorporated into an on-line data base known as the Integrated Risk Information System (IRIS). There are currently 260 substances in the IRIS system, and 120 soon will be added.

The Rfd workgroups' efforts reportedly focus on the first two steps of the risk assessment process specified by NAS: hazard identification and dose-response assessment. The remaining two tasks (i.e. exposure assessment and risk characterization) are performed independently by the various program offices. As a result, because of different exposure assumptions regulatory standards developed within different program offices for the same substance may be different, even though the same Rfd value was used to develop the standard. For example, the Office of Drinking Water uses a standard 20% source contribution assumption in the development of its standards. As a result, the Rfd

is multiplied by 20% in the Drinking Water Office to develop a drinking water standard. In contrast, the Office of Solid Waste has used a 25% relative source contribution assumption.

3) Threshold Limit Values and the Inhalation Rfd Workgroup

Rfds or ADIs have generally been based on studies where the route of exposure was via ingestion or dermal contact. Differences in the dynamics of the respiratory system across species raise questions regarding the appropriateness of using orally derived Rfds in inhalation contexts (although Rfds have been occasionally applied in such contexts - see Program Office sections below). The Rfds verified by the inter-office workgroup are intended for oral and dermal exposure situations. However, an additional workgroup has been formed within EPA to study the questions relevant to the derivation of inhalation Rfds, and to develop verified inhalation Rfd values. The workgroup is currently in the process of drafting guidelines for the development of inhalation Rfds.

The problems of applying Rfds in the inhalation context has resulted in some consideration being given to Threshold Limit Values (TLVs), which are developed by the American Conference of Governmental and Industrial Hygienists. TLVs were intended for use in determining protective levels for healthy workers from exposure to airborne contaminants within the work environment. TLVs

comprise a large body of toxicological, epidemiological, and clinical information pertaining to human exposure to airborne contaminants.

TLVs have been used within EPA to support primary risk assessment data; however, the values have not been used alone as the basis for a regulatory decision. There have been suggestions that TLVs could be used to derive Rfds; however, the Agency has decided not to endorse the general use of TLVs in deriving Rfds (EPA, 1988g). The chief problems associated with TLVs are: 1) the values may not be established based on chronic effects and may differ from Rfds in severity of effect, 2) the evaluation of toxicity data by agencies deriving TLVs may differ from that of EPA with respect to the weight of evidence classification, application of uncertainty factors, and other issues, 3) the most sensitive and heterogenous general population are not considered, 4) occupational levels are usually, but not always set below levels expected to produce effects, 5) the ACGIH specifically states that it is inappropriate for occupational levels to be used as limits for non-workplace environments (EPA, 1988g; EPA, 1987g). Nevertheless, the EPA indicates that the data base supporting the TLV could be evaluated on a case by case basis, in the absence of specific pertinent animal data (EPA, 1988g).

B) Dose-response Modelling

Dose-response modelling involves the use of

mathematical functions to characterize dose-response relationships. To date the use of dose-response models in non-cancer assessments has been limited. The Office of Air and Radiation is the only Office using models to evaluate the dose-response relationship. As mentioned earlier, modelling in non-cancer assessments has not involved low-dose extrapolation, because of the lack of knowledge regarding animal to human sensitivity. As a result, the models utilized by the Air Office have employed only human data.

C) Advantages and Disadvantages of Dose-response Modelling and the Rfd Approach

The advantages of modelling dose-response relationships are: 1) a description of the shape of the dose-response curve (A steep curve indicates that there will be large increases in response from small increases in dose, while a shallower curve indicates that large dose increases can be tolerated without causing a widespread response. Such considerations are relevant to regulatory 'margin of safety' determinations); 2) quantification of the uncertainty associated with dose-response values (This quantification of uncertainty avoids the implication that the dose-response values are "safe" values).

The chief disadvantage of using models are: 1) the time and expense involved in meeting the data requirements; 2) the currently uncertain use with animal

data.

The advantages of the Rfd method are: 1) longest history of use within EPA and other organizations; 2) workgroup review (discussed below); 3) relatively inexpensive with few data requirements. Disadvantages of the Rfd method are: the slope of the dose response curve is not considered, since only one data point is relied upon; 3) this one data point is as easily influenced by study design (i.e. the number of subjects within the bioassay as well as the dose level studied) than by the dose-response curve data; 4) no estimate of the incidence or percentage response associated with a particular exposure is possible; 5) the value may falsely imply safe and unsafe levels; 6) the use of the technique has uncertain application to the assessment of acute exposures.

II. <u>DOSE-RESPONSE ASSESSMENTS WITHIN EPA PROGRAM OFFICES</u>

A) Office of Drinking Water (ODW) - <u>Safe Drinking Water Act</u> (SDWA).

Section 1412 of the Safe Drinking Water Act requires EPA to promulgate National Primary Drinking Water Regulations (NPDWRs) and Maximum Contaminant Level Goals (MCLGs). MCLGs are to be set at a level which no known or anticipated adverse effects on the health of persons occur, and which allows for an adequate margin of safety (Section 1412 (b)(4)). MCLGs are considered nonenforceable health

goals (EPA 1987c).[6] NPDWRs include maximum contaminant levels, which are to be set "as close to the maximum contaminant level goal as is feasible" (Section 1412 (b)(4)).

To set MCLGs the ODW utilizes the Rfd approach to perform dose response assessments (EPA, 1985a). The ODW is currently in the process of proposing revised regulations for 9 inorganic chemicals and 30 synthetic organic chemicals. According to ODW, these proposed MCLGs are the first which are based on numbers which have been "verified" by the Rfd workgroup.[7]

1) Health Advisories

In addition to MCLGs and MCLs the ODW also issues non-enforceable Health Advisories (HA). HAs represent guidance levels for drinking water exposures comprising one-day, ten-day and longer-term exposures (the HAs do not take into consideration other exposures from food or air). HA values are not used to establish drinking water standards. Rather they are intended as informal scientific guidance to

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[6] The SDWA was amended by Congress in 1986. The '86 amendments changed what was known as an "Recommended Maximum Contaminant Levels" (RMCL) to a MCLG; however, the designation change did not imply any substantive change in the law. (sec 1412 (a)(1) and 00083).

[7] Prior to the formation of the Rfd workgroup the ODW developed its own Rfds, while relying on advice from the National Academy of Sciences other scientific groups, and the public (see EPA, 1985 and 1985a).

municipalities and other organizations when an emergency spill or other contamination situations occur.

HAs are calculated for substances which have received MCLGs, and for substances which do not yet have standards. The ODW has been developing HAs for approximately ten years, in response to the great demand for information on acute exposures.

The HAs are derived using an Rfd approach (NOAEL divided by uncertainty factor). The data used for HA derivations are generally from studies of comparable duration to the specific HA time period.

2) Uncertainty Factors Applied to Class C Carcinogens

In November of 1985 The ODW issued a final rule which set RMCLs for eight volatile synthetic organic chemicals (VOCs) (EPA 1985a). One of these VOCs was 1,1-dichloroethylene (1,1-DCE or vinlidene chloride). Data demonstrated acute and chronic systemic effects from the compound, as well as some indication of carcinogenicity. Based on a weight of evidence determination the ODW decided to classify 1,1-DCE as a Class C carcinogen. However, the MCLG for 1,1-DCE was based on an ADI calculation, rather than traditional carcinogenic modelling approaches. An additional uncertainty factor of ten was used in the ADI calculation to protect against possible carcinogenic

effects.[8]

The decision to use the additional 10 fold uncertainty factor for 1,1-DCE occurred at a March 1, 1985 Option Selection meeting concerning ODW's final RMCLs, chaired by Deputy Administrator, A. James Barnes. Barnes'decision affirmed ODW's recommendation to base RMCLs for Class C carcinogens on either an ADI with an additional safety factor, or on an extrapolation to an incremental lifetime risk in the range of 10^{-5} to 10^{-6} using a conservative model (EPA, 1985b). The ODW indicated that whenever the data were adequate the extrapolation to incremental lifetime risk should be performed. Decisions to use either of the two methods would be performed on a case by case basis, depending on the quality of the data.

The Natural Resources Defense Council (NRDC) filed suit in the United States Court of Appeals for the District of Columbia Circuit challenging the EPA Group C policy, specifically for 1,1-DCE. The NRDC charged that the EPA should treat Group C substances similarly to Group A or B carcinogens and set a health goal of zero. In addition, the NRDC thought the use of an additional 10-fold uncertainty factor was arbitrary and capricious.

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[8] The EPA classifies carcinogens in five categories (A through E) based on a weight of evidence determination. Class C carcinogens are considered "Possible Carcinogens", because of limited evidence of carcinogenicity. (EPA, 1986a). Class C is a near borderline classification, and consequently there is significant doubt regarding the carcinogenicity of such substances.

The Court of Appeals upheld the decision of the Agency and denied the petition filed by NRDC (NRDC v. EPA, CADC, 824 F2d 1211). The Court stated that the EPA was correct in considering the carcinogenicity evidence for 1,1-DCE, and accounting for it, "at the 'adequate margin of safety' stage." The Court concluded that "this is neither an unreasonable interpretation of the statute nor an unwise choice of policy."

The ODW is the only program office known to use the Class C carcinogen policy described above.[9] The ODW claims that the application of the extra 10-fold factor has resulted in MCLGs which are within acceptable cancer risk ranges, if the substances had been regulated as carcinogens. Other substances where the Class C policy was used include: monochlorobenzene, styrene, lindane, and p-dichlorobenzene.[10]

3) Use of Modifying Factor

As indicated above, the modifying factor (MF), is an additional uncertainty factor which can be greater than zero and less than or equal to 10. The magnitude of the MF is dependant on the professional assessment of the

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[9] The Rfd Workgroup does not consider the Class C policy as part of the Rfd risk assessment process, but a decision within the boundaries of risk management. In addition, other program offices have disputed the ODW's policy (e.g. the Office of Air and Radiation nonconcurred with ODW's p-dichlorobenzene standard).

[10] Styrene has since been reclassified as a Class B carcinogen.

available data base used for the Rfd. The EPA makes the following comment on the invocation of the MF:

"Such practices, as employed by a number of scientists in different programs/agencies, exercising their best scientific judgment, have in some cases resulted in different ADIs for the same chemical. The fact that different ADIs were generated (for example, by adopting different SFs) can be a source of considerable confusion when the ADIs are used exclusively in risk management decision-making. The existence of different ADIs need not imply that any of them is more "wrong"--or "right"--than the rest. It is more nearly a reflection of the honest difference in scientific judgment" (EPA, 1988h).

Verified Rfds (by the Rfd workgroup) aim to develop consistency across the Agency with respect to the Rfd value. Such consistency includes an agreed upon use of uncertainty factors. The guidelines for the application of these uncertainty factors attempts to aid in reaching this consistency. However, the use of the modifying factor allows for consideration of factors not otherwise covered by the guidelines. It is worth examining the use of the modifying factor to understand the types of considerations made in the final Rfd calculation. The Rfds used for the ODWs's MCLGs provide a number of examples which illustrate these considerations (including a case where no uncertainty factor was applied). These examples are described below.

a) Sensitive Subgroups

Barium - When the ODW proposed an RMCL for barium in 1985, the data was scant and subject to misgivings. The RMCL was based on a 100 mg/l LOAEL derived from a rat study. The ODW

recognized that an ADI based on an animal LOAEL traditionally utilized 1000 fold uncertainty factor. However, the study "minimized exposure of the rats to trace metals (i.e. calcium)," which was believed to have contributed to the effects observed in the rats. As a result, the ODW decided to apply a smaller uncertainty factor of 100.

Subsequent to the 1985 proposed RMCL, the EPA conducted a 10 week human study, which measured cardiovascular risk factors from ingested barium via drinking water. The study identified adverse effects at 10 mg/l. The MCLG for barium currently being considered for reproposal by the ODW incorporates an uncertainty factor of 2 to arrive at an MCLG of 5 mg/l. The ODW indicated that normally an uncertainty factor of 10 should have been applied (to account for variations in sensitivity within the human population). However, the smaller uncertainty factor was used because the ODW believes that the results of the more recent study was corroborated by the results of earlier human studies (i.e. the Brenniman et al. 1981 study[11]), and the value was essentially consistent with the 4.7 mg/l level recommended by the NAS.

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[11] The Brenniman study had actually been considered suspect by the ODW in the 1985 proposed RMCL for barium, because of confounding variables, uncontrolled parameters and data inconsistencies.

Nitrate - The ODW did not apply an uncertainty factor in arriving at its standard for nitrate. The ODW claimed to base its nitrate standard on a survey of literature (Walton, G. 1951. "Survey of Literature Relating to Infant Methemoglobinea Due to Nitrate Contaminated Water." Am. J. Pub. Health 41:986-996). The survey concluded that while serious methemoglobinemia[12], leading to death in some cases, was observed in infants exposed to high levels of nitrate, no such cases were observed in infants exposed to 10 mg/l or less of nitrate. The ODW claimed that at 10 mg/l of nitrate,

"there would be no adverse effects and would allow an adequate margin of safety, because the available studies provide no evidence that any adverse health effect is seen at nitrate levels of 10.0 mg/l or below."

The ODW cited additional studies which corroborated the finding of a 10 mg/l NOAEL.

The ODW mentioned that the EPA normally applies a ten-fold uncertainty factor when an MCLG is based on human data, in order to protect the most sensitive members of the population. The ODW chose not to apply such an uncertainty factor in setting the MCLG for nitrate, because, "the standard is designed to protect the most sensitive population (i.e. infants), and the standard has been in

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[12] Methemoglobinemia is a condition involving the chemical alteration of hemoglobin, which limits the availability of oxygen to the tissues (known in infants as: "blue baby syndrome").

effect in this country for decades and no cases of methemoglobinemia have been reported in public drinking water supplies [sic]." (EPA, 1988f).

In response to public comments which criticized the 1985 nitrate standard as too high, the ODW responded that an adequate margin of safety was present in the standard, "based on the extensive review of the literature and decades of experience with the current nitrate standard." (EPA, 1988f). There is still some debate within the EPA regarding the ODW's nitrate standard.

b) Balancing Adverse and Beneficial Effects

Selenium - ODW's standard for selenium (.045 mg/l) is based on a LOAEL (3.2 mg/l) derived from a human study, and evidence that selenium may be an essential nutrient. An uncertainty factor of 15 was used to derive the standard, although ordinarily a 100 fold uncertainty factor is applied when using a LOAEL from a human study. The ODW indicated that if it applied an uncertainty factor of 100, the resulting DWEL would be below .05, which was the level specified as an adequate and safe level by the National Academy of Sciences. The ODW was concerned about setting a very low standard for selenium, because of selenium's recognized essentiality in the human diet. As a result, the ODW tried to balance selenium's beneficial and adverse effects by adjusting the uncertainty factor:

" Thus an uncertainty factor of 15 appears to be adequate to provide a balance between adverse effects and beneficial effects in humans ." (EPA, 1985c)

The above statement indicates that perhaps the uncertainty factor was used by the ODW to adjust the Rfd value to obtain consistency with NAS recommendations.

B) Office of Water (OW) - Clean Water Act

Section 304 (a)(1) of the Clean Water Act directs EPA to develop water quality criteria, which include: "the kind and extent of all identifiable effects on health and welfare...". (EPA, 1980). The Office of Water (OW) has been publishing water quality criteria since 1973. The latest water quality criteria documents were published in 1986 (EPA, 1986). The criteria are used in the derivation of regulatory standards under water quality based effluent limitations under section 302, water quality standards under section 303, and the toxic pollutant effluent standards under section 307.

The health assessment portions of the criteria documents establish ambient water concentrations which, in the case of non-cancer effects, "are not expected to produce adverse health effects in humans" (EPA, 1986 - Appendix B). Health criteria are derived based upon verified Rfds.

The Section 304 water quality criteria are conceptually similar to the MCLGs derived under the SDWA

(EPA, 1980). However, values obtained for a substance under Section 304 or the SDWA may differ based on varying exposure assumptions. Section 304 requires that the criteria take into account exposure resulting from the ingestion of fish. This assumption affects the final water criteria value, since Rfds are divided by exposure values to obtain the final criteria value. Such assumptions are not made in developing MCLGs pursuant to the SDWA. A standard 20% drinking water contribution is assumed in the calculation of MCLGs.

C) Office of Pesticide Programs (OPP) - Federal Insecticide, Fungicide, and Rodenticide Act; Federal Food, Drug and Cosmetic Act

The OPP registers pesticides pursuant to Section 3 of FIFRA and sets food tolerances for pesticides pursuant to Sections 408 and 409 of the FDCA.

1) Registration

Under Section 3 (a) of FIFRA all pesticides must be registered with the EPA. FIFRA requires the EPA to deny a pesticide registration if it determines that a pesticide generally causes unreasonable adverse effects on the

environment."[13] Registrations expire after five years, and reregistration is necessary to continue use of a pesticide. (7 USC 136d)

While undergoing registration or reregistration a pesticide may trigger the special review process if the EPA believes that a pesticide may cause unreasonable adverse effects on the environment. (40 CFR 154.1) The process is intended to help the Agency determine if the registration of a pesticide should be cancelled, denied or reclassified. The Department of Agriculture, the Scientific Advisory Panel (SAP), the EPA, and the public participate in the special review process (EPA, 1985e). Criteria for determining "unreasonable adverse effects" for new and previously registered pesticides are given in 40 CFR 162.11, and 40 CFR 154.7. Included in these effects are acute injuries and chronic toxicity.

2) Food Tolerances

The second main task of OPP is to establish food tolerances for pesticide residues. A food tolerance is the maximum residue level of a pesticide allowed in or on a raw agricultural commodity or processed product. EPA's

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[13] This term means any unreasonable risks to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of the pesticide. (7 USC 136 (bb)).

authority to establish such tolerances is granted under section 408 and 409 of the Food Drug and Cosmetic Act. The OPP also requires that food tolerances be set for a pesticide which is designated for use on food crops before it approves the pesticide's registration. Enforcement of tolerances is performed by the Department of Agriculture and the Food and Drug Administration.

Section 408 of the Act concerns pesticide residues in raw agricultural commodities. The tolerances set pursuant to section 408 are to protect the public health, while considering the need for "an adequate, wholesome and economical food supply." As in FIFRA, section 408 requires EPA to consider the potential benefits of a pesticide when setting tolerances. However, it is claimed that the OPP has rarely considered benefits in its tolerance setting procedure, because dietary contributions from such tolerances are rarely found to exceed the ADI (National Research Council 1987, p. 32). Section 409 concerns pesticide residues in processed foods, and utilizes a risk based standard, and has been interpreted to exclude economic considerations or other benefits (National Research Council 1987, p.26).

Food tolerances are set based on results of field trial data. A tolerance level is proposed by a petitioner which reflects the maximum residue likely to occur as a result of the proposed use (EPA 1987, p.5). The next step

is to calculate the increase in human exposure to the pesticide resulting from the tolerance quantity (the residues from the proposed use are added to existing use residues). This quantity is compared to an ADI for the pesticide. If the total exposure (ingestion via food) exceeds the ADI the tolerance is denied or means of lowering the tolerance are explored.

3) Dose-response Assessment

The OPP assesses risks from non-cancer health effects, in the context of registrations or setting food tolerances, using the Rfd approach. In 1985 the Hazards Evaluation Division circulated written guidelines for determining ADIs (Farber 1985). The procedures and methods outlined in the guidelines were supported by interviews with OPP personnel. The guidelines follow the Rfd approach, but utilize different terminology. The guidelines calculate an ADI based on the lowest NOAEL and the appropriate safety factor, usually 100 or 10 if the NOAEL is based on cholinesterase inhibition.[14] Other safety factors are used with "proper justification".

The OPP makes an explicit distinction between

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[14] The guidelines do not indicate why a 10 fold safety factor is appropriate in the case of cholinesterase inhibition. Sources within OPP indicate that there is significant human data for substances exhibiting cholinesterase effects, and therefore the 10 fold factor is used to account for varying sensitivities within the population. Other OPP sources indicate that it is generally known that there is no variation in sensitivity between animals and man regarding cholinesterase inhibition effects.

provisional ADIs and regular ADIs. An ADI is established for a pesticide only if the following fully acceptable studies are available:

1 rat chronic study

1 dog chronic study

1 reproduction study

2 teratology studies

Provisional ADIs (PADIs) are established if the data base is incomplete. 100-fold and 1000-fold safety factors are used to calculate the PADI depending on the adequacy of the data (i.e. the poorer the data the greater the safety factor used). OPP defines a LOAEL as a "minimal effect at the lowest dose". An ADI based on a LOAEL is referred to as a Preliminary Limiting Dose (PLD). The PLD is considered, "the best possible approach to provide an exposure level of relatively low concern, including a wide variety of uncertainties." PLDs are also used when subchronic studies are used in place of chronic studies. The OPP also allows for the use of additional safety factors to account for uncertainties on a case-by-case basis.

An example of the OPP's use of the Rfd approach is described in the case study discussed near the end of the program office sections.

D) Office of Toxic Substances (OTS) - Toxic Substances Control Act (TSCA)

Section 6(a) of TSCA directs the Administrator to regulate the manufacture, processing or use of a substance if, "there is a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use or disposal ... presents or will present an unreasonable risk of injury to health or the environment."[15] Such activities are to be regulated, "to the extent necessary to protect adequately against such risk using the least burdensome requirements" (Section 6 (a)). Section 5, paragraphs (e) and (f) also allow the Administrator to take similar actions for new chemicals or existing chemicals which have proposed "significant new uses."

The Act requires that EPA consider the following factors in assessing unreasonable risk: the chemical's effect on health and the environment and the magnitude of human and environmental exposure to it; the benefits provided by various uses of the chemical; the availability of substitutes for the chemical for such uses; reasonably ascertainable economic consequences of regulating the chemical after consideration of the effects of such regulation on the national economy, small business,

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[15] TSCA also directs the Administrator to use other laws administered by EPA to protect against unreasonable risks unless the Administrator determines that it is in the public interest to protect against such risks under TSCA. (TSCA, Section 9 (b)

technological innovation, the environment, and public health (TSCA, Section 6 (c)(1).

In addition to giving EPA authority to prohibit or restrict chemical manufacture, processing, etc., the Act also grants the EPA authority to require testing of existing or new substances for health effects. Tests of new substances or significant new uses of existing substances are required to be submitted with a pre-manufacturing notification (Section 5). Additional testing of existing substances is required pursuant to Section 4 whenever such chemicals "may present an unreasonable risk of injury to health or the environment ... will be produced in substantial quantities ... [and] there is or may be significant or substantial human exposure to such substance or mixture."

1) New Chemical Assessment

EPA's decision for taking regulatory action on a new substance is based on judgments about: the substance's potential toxicity based on its structural similarities to existing chemicals whose toxicity is known; and the manner and extent to which people and the environment are likely to be exposed to the substance when manufactured and used as specified in the premanufacture notification (GAO, 1984). The structure activity analysis is relied on, because chronic toxicity data is not developed for new chemicals prior to their manufacture. However, once an

analog is identified the OTS assess risks from the new substance in the same way that it assesses risks from existing chemicals.

2) Existing Chemical Assessments

Sources within the Office of Toxic Substances indicated that generally the Office strives to model a dose-response curve to describe the dose-response relationship. A model was considered to provide the best representation of the dose-response relationship. However, in most cases there is insufficient data to construct such a model. As a result, the Office usually will rely on an Rfd calculation when assessing the dose-response relationship. However, the components of the Rfd calculation (i.e. NOAEL uncertainty factor) will frequently be incorporated into a margin of safety calculation. Two examples of dose-response assessments performed by the OTS are described below. These examples are: glycol ethers and formaldehyde.

3) Glycol Ethers

OTS issued an advance notice of proposed rulemaking for two glycol ethers and their acetates on January 24, 1984 (EPA, 1984). A risk assessment was completed for the substances in December of the same year (EPA, 1984a). The health endpoints of concern were developmental and testicular toxicity. The OTS relied on the margin of safety approach in considering the dose response relationship.

One outcome of the risk assessment for glycol ethers was the precise identification of the sensitivity difference between rats and humans in terms of testicular effects. Testicular effects were measured in terms of reductions in sperm counts. It was determined that humans exhibited the same reduction in sperm counts at one-twentieth the dose of rats. In addition, it was also determined that such a reduction of sperm counts will also have a greater effect on fertility in humans than it does in rats. As a result, the OTS report concluded that: "Therefore a considerable margin of safety is required to prevent reduction in human fertility." The fact that human sensitivity was demonstrated to be greater than rats by a factor of .05 suggests that the standard ten-fold uncertainty factor used to extrapolate from animals to humans should have been increased to twenty (resulting in a total safety factor of 200 when interspecies variability is included). However, the OTS did not suggest such a margin of safety. Instead, the OTS identified a 100-fold margin of safety as the generally acceptable value.[16]

"To assure chemical safety it has been standard Agency practice to establish a margin of 100 to allow for the possible greater sensitivity and variability of humans over experimental animals...
The Agency has analyzed the specific data on these glycol ethers and believes that a margin of safety of 100 is

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[16] Although a 100 margin of safety was identified, the OTS also indicated that perhaps a greater margin of safety would be necessary to prevent all developmental effects in humans (EPA, 1984a).

necessary to be reasonably confident of no human effects." (EPA. 1986d).

A source at the OTS indicated that although the data seemed to indicate that a margin of safety larger than 100 was appropriate, the OTS felt more inclined to defer to standard Agency policy of using a 100-fold margin of safety when extrapolating from animal data.

The OTS has since referred the glycol ethers matter to the Occupational Safety and Health Administration (EPA, 1986d).

4) Formaldehyde

In May 1984 EPA announced that formaldehyde would be reviewed as a toxic substance pursuant to Section 4(f) of TSCA. The primary endpoint of concern was cancer; however, the OTS decided to consider non-cancer effects from formaldehyde because, "...other effects should be considered in any action to reduce health effects from HCHO [formaldehyde]" (EPA, 1987h). The major non-cancer effects associated with formaldehyde were sensory irritation and cellular change (the latter being far less evident). Both effects were considered to exhibit a threshold response.

The OTS issued its risk assessment for formaldehyde in April 1987 (EPA, 1987h). One of the purposes of the report was to determine if a dose-response 'pattern' (i.e. curve) in the human population could be determined. The OTS

believed that, "while many of the effects [from formaldehyde] are well documented, the dose-response patterns in the human population are not." The OTS intended to develop a dose-response curve using human data.

The risk assessment report cited studies which apparently constructed a dose-response curve. However, upon reviewing the data the OTS concluded that population risks for the irritant effects could not be quantified. The OTS found what it thought were serious flaws in the design of the studies providing the data. However, the OTS indicated that the data does provide a qualitative estimate of population response over a wide exposure range. This qualitative relationship was represented by a range of exposures which would produce the irritative effects.

The OTS tried to construct a dose-response curve, thinking that the available data was sufficient to do so. As indicated earlier, the OTS believes that a dose-response curve should be constructed for systemic effects when there is adequate data. The basis for this policy could not be identified. However, there is the belief within OTS that dose-response curves represent "good science".

E) Office of Solid Waste (OSW) - Resource Conservation and Recovery Act (RCRA)

Section 3004 (a) of the Resource Conservation and Recovery Act requires the EPA to promulgate regulations

establishing performance standards for owners or operators of facilities for the treatment, storage or disposal of hazardous waste, which will protect human health and the environment. The OSW regulates and is proposing to regulate a number of facilities pursuant to this section including: boilers and industrial furnaces.

In 1987 OSW proposed to base permit requirements for industrial boilers and furnaces on national performance standards with provision for risk based variances, rather than solely on site-specific risk assessments for every facility. The OSW assesses the risk from emissions from such facilities by comparing exposures to a Reference Air Concentration (RAC). The RACs are derived from verified oral Rfds.[17] The Office intends to utilize the inhalation Rfds, once they are developed by the Inhalation Workgroup. The Office relied on the oral Rfds to calculate the RACs primarily as a result of the review afforded the verified Rfds (see EPA, 1987e).

Studies conducted during the development of the '87 boiler and furnace regulations (EPA, 1987f) examined the use of threshold limit values (TLVs) and Rfds in calculating maximum annual average concentrations and developing screening concentrations (i.e. concentrations which serve as indicators of possible hazards). However,

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[17] However, in the case of hydrogen chloride inhalation values were based on inhalation data (EPA, 1986c).

the OSW recognized the Agency preference for Rfds:

"During development of the proposed rule for boilers and industrial furnaces... the Agency formed an Inhalation Rfd Workgroup to examine issues associated with exposure via inhalation and to develop inhalation Rfds. Consequently, although this document considers TLV health limits, the proposed rule is based on a consideration of only oral-based Rfd endpoints."

In the May '87 regulations (EPA, 1987e) the OSW stated that the oral Rfds were relied upon to derive the RACs, because: of EPA's commitment to establishing Rfds; the values are subject to extensive review via the verification workgroup; the quality of the data is high and the fact that the most sensitive individuals are taken into consideration.

The OSW has also proposed Reference Air Concentrations (RACs) for short-term or less than life-time exposures. In the 1987 regulations the EPA stated:

"...during the annual exposure, the periods of exposure to high concentrations are balance by periods of exposure to low concentrations as wind speed and direction varies. Thus maximum annual average concentrations are always much lower than short-term exposure concentrations. On the other hand, the short-term exposure RAC is also generally much higher than the life-time exposure RAC. Nonetheless, in some cases, short-term exposure may pose a greater health threat than annual exposure" (EPA, 1987e).

The OSW decided to base short-term assessments on lifetime inhalation exposure limits, claiming that such an approach is appropriately conservative. Reasons given for relying on the lifetime values are: the limits are sufficiently protective for lifetime exposures and

certainly protective for exposures of shorter duration; the direct derivation of short-term exposure limits for the majority of constituents is not possible because of a lack of acute inhalation data (Chow, 1987). The only constituent which the OSW proposed a short-term RAC for was hydrogen chloride (EPA, 1987e).

F) Case Study - Aldicarb

The Office of Air and Radiation is the final program office whose dose-response assessment will be reviewed. The Air Office has not relied on the standard Rfd methodology used by all of the program offices described above. As a result, before reviewing the Air Office's methodologies, a more detailed comparison will be made of how program offices have applied the Rfd approach. This comparison will be performed through use of the pesticide aldicarb as a case study. The program offices which regulate (or intend to regulate) aldicarb include the OPP and the ODW.[18]

Despite internal EPA efforts to obtain consistent Rfd values, individual program office precedent has succeeded in influencing the calculation of the Rfd value. The influence of this precedent is illustrated by the ODW's and

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[18] There are other individual substances which have been regulated by at least two different program offices. Aldicarb has been chosen as the case study, because its assessment readily demonstrates the tension between program office precedents and Agency-wide policies in the Rfd process.

OPP's calculation of an Rfd for aldicarb.

Aldicarb is a carbamate known to induce cholinesterase inhibition during acute exposures. The OPP and ODW are in the process of developing regulations for aldicarb. In 1988 the OPP issued a preliminary determination regarding the cancellation of aldicarb registrations (EPA, 1988). The ODW proposed a RMCL for aldicarb in 1985 and is currently in the process of reproposing an MCLG for aldicarb (EPA, 1985; EPA, 1988f). The Rfd for aldicarb has been verified by the Rfd workgroup, and the Rfd used by the two offices is consistent with the workgroup's value. The difference between the two Offices regarding the aldicarb Rfd lies in how each Office calculated the final value.

The OPP and the ODW utilize different NOAELs and different uncertainty factors to arrive at the same Rfd. The ODW utilized a NOAEL of 0.125 mg/kg and a 100 fold uncertainty factor - due to animal to human extrapolation, and to protect the more sensitive subgroups in the population (EPA, 1985d). The NOAEL was based on a 6-month feeding study in rats. These values are consistent with the values used by the Rfd workgroup.

The OPP's discussion of the aldicarb Rfd calculation is contained within the Office's aldicarb special review technical support document (EPA, 1988l). A human NOEL of 0.01 mg/kg was identified, and a 10 fold uncertainty factor was used to account for inter-subject variability. However,

the human NOEL was not derived from a particular study.

The OPP obtained its NOEL by first relying on a human study (Dernehl and Block, 1971) which identified a LOEL and NOEL for aldicarb at 0.1 mg/kg and 0.05 mg/kg, respectively. However, the OPP indicates that the estimated doses from the study were uncertain, because only four subjects were used per dose. The OPP indicated that incidents of accidental exposures suggest that the values identified in the Dernerl and Block study were probably too high. With little additional basis for its decision the OPP concluded that:

"...the Agency believes that the NOELs for Che inhibition are close to 0.01 mg/kg; and that at 0.001 mg/kg, it is unlikely that many individuals will show clinical signs or have depressed Che activity" (EPA, 19881).

Public comments on Position Document 1 published in July 1984 requested clarification of the calculation of the ADI, and that a fuller description of the different ADI's for aldicarb be provided (EPA, 19881). The OPP responded that the ODW selected an ADI for aldicarb based on a NOEL of 0.12 mg/kg, and the use of a 100 fold uncertainty factor. The OPP claimed that the ODW used the 100 fold uncertainty factor because of aldicarb's extremely steep dose-response curve, high acute toxicity and possibility of concurrent exposure to other acetylcholinesterase inhibitors in the diet. However, there is no evidence that such was the ODW's basis for employing

the 100 fold uncertainty factor.[19] Instead, the ODW claimed that the 100 fold uncertainty factor: 1) was in complete consonance with the guidelines for a 100-fold safety factor adopted by the National Academy of Science, and 2) assured protection of suspected greater fetal sensitivity (EPA, 1985d).

The disparity between the ODW and OPP calculations of the aldicarb Rfd can be linked to policies that the two offices inherited from other programs. The National Academy of Science was originally given the responsibility of developing criteria for drinking water regulations. In 1977 the NAS published Drinking Water and Health (NAS, 1977). Many of the ODW's justifications for its MCLGs refer to the NAS's standards. The ODW appeared to adjust its use of the uncertainty factor to align the proposed selenium and nitrate MCLG with the NAS recommended standard (see sections II(A)(3) a and b above). As indicated above, the Drinking Water Criteria Document for aldicarb cited the 100 fold uncertainty factor as consistent with NAS guidelines.

The OPP inherited many of its procedures and policies

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[19] The ODW's revised drinking water regulations (EPA, 1988f) did not provide such a rationale for the use of a 100 fold uncertainty factor for aldicarb. In fact, the OPP special review document was the only evidence that consideration was given to the dose-response curve. The OPP indicated that the lowest dose which produced clinical signs in a rat study (Maripot, et al. 1980) also killed two of the ten rats. A human study described by the OPP demonstrated severe clinical signs in the higher of two doses which were only 0.24 mg/kg apart. The OPP claimed that these studies indicated a very steep dose-response curve.

from the Food and Drug Administration and the Dept. of Agriculture. As indicated earlier the ADI technique was first used to determine toxic properties of food additives. The OPP inherited responsibility from these other agencies by determining the toxic properties of pesticide residues in food. These Agencies have long considered cholinesterase inhibition responses to be the same in animals and in man (i.e. no greater sensitivity in man). Consequently, these Agencies have considered a 10 fold uncertainty factor sufficient in determining ADIs for cholinesterase inhibitors. As indicated earlier, the OPP's explicitly stated that its policy is to apply a 10 fold uncertainty factor when cholinesterase inhibition is the effect of concern.

The above case study demonstrates that some program offices are experiencing pressure to maintain two types of consistency in their dose-response assessments. This consistency is in terms of adherence to precedent (consistency over time) and adherence to Agency verified Rfd values (consistency across the Agency). The incentives to maintain regulatory consistency over time are great. Severe disruptions can occur from the lowering of a regulatory standard. For example, the closing of entire communities in Nevada was threatened by the lowering of the nitrate drinking water standard. Apparently, these communities had high background levels of nitrate in their

water supplies, and had been drinking the water for many decades. Alternative sources of drinking water were considered unavailable in the arid regions where these communities are located. It is reasonable to suspect that the OPP would receive severe criticism from pesticide manufacturers if a larger uncertainty factor was employed in place of the longstanding policy of applying a 10 fold uncertainty factor when cholinesterase is the effect of concern.

The EPA's concern for Rfd consistency across program offices stems from the Agency's strong intention to keep scientific determinations distinct from policy decisions. The EPA is attempting to prevent policy considerations from entering into the risk assessment process through the Rfd verification process. The possibility of a program office inadvertently bending the outcome of its risk assessments to meet policy needs will hopefully be reduced as a result of the review of all program offices in the workgroup. However, whether the Rfd workgroup has been successful in avoiding such skewed risk assessment outcomes is uncertain. It has been suggested that a few program offices have been driving the Rfd process. Additional research regarding the verification process is necessary.

G) Office of Air and Radiation (OAR) - Clean Air Act.

1) National Ambient Air Quality Standards (NAAQS)

Section 108 of the Clean Air Act authorizes the EPA to set Primary National Ambient Air Quality Standards for emissions which:

"...cause or contribute to air pollution which may reasonably be anticipated to endanger public health ...(and) the presence of which in the ambient air results from numerous or diverse mobile or stationary sources."

Section 109 describes how the standards should be set:

"the attainment and maintenance of which in the judgment of the Administrator, based on such criteria and allowing an adequate margin of safety, are requisite to protect the public health."

Primary standards promulgated under Sections 108 and 109 exclude economic and technological feasibility considerations. However, States are given primary responsibility for attainment of the standards, and may consider economic and technological considerations in developing their implementation plans (SIPs). Further guidance in the legislative history of the Act indicates that the standards should be set at "the maximum permissible ambient air level...which will protect the health of any (sensitive) group of the population" (U.S. Senate, 1979).

The OAR has been exploring alternative risk assessment methods since the late 1970's. In 1979, at the request of the Office of Air Quality Planning and Standards (OAQPS- a division within OAR) the EPA's Science Advisory Board (SAB) established a subcommittee to review risk assessment methods being used or being developed with regard to the

NAAQS for ozone. At the time the OAQPS was considering a decision-analytic approach for the ozone assessment. The Subcommittee recommended that the OAQPS continue to develop and evaluate additional risk assessment methods, and that it postpone the use of the decision-analytic method until further review of the technique occurred (EPA, 1983). As a result, the OAQPS has continued to explore alternatives to its risk assessment methods.

The types of risk assessment techniques which the OAQPS has explored are generally considered to be much more resource intensive than techniques used in other parts of the Agency. The use of these resource intensive techniques has been attributed to the expense imposed on the regulated population by the NAAQS. The following estimated breakdown has been offered by the EPA of incremental pollution abatement expenditures[20]:

1986 $Billions

Program	1979 Total Costs	1988 Total Costs	1979-88 Total Cum.Costs
Air	32.5	54.8	435.7
Water	18.5	35.5	247.2
Solid	<.1	3.4	22.4
Toxics	.4	1.6	11.9
Drinking Water	<.1	.6	3.9
Noise	.1	2.3	10.1
Pest.	.1	.1	1.7
Land Rec.	2.0	2.2	22.3
Total	53.8	100.5	755.3

[20] from Principles of Economic Analysis Briefing Paper presented during EPA Risk Analysis and Decision-making seminar. August 1988.

The proportionately higher costs in the Air program are considered responsible for the level of effort at the OAQPS in conducting its risk assessments. William Ruckleshaus alluded to the need for such precise standards during a speech at Princeton:

"...If I am going to propose controls that may have serious economic and social effects, I need to have some idea how much confidence should be placed in the estimates of risk that prompted those controls." (Ruckleshaus, 1984).

The OAQPS is pioneering dose-response assessment approaches within EPA. These approaches involve dose-response modelling along with decision-analytical techniques. The use of these methods in the development of the NAAQS for ozone and lead are described below.

a) Ozone

The ozone NAAQS (currently under review) utilizes mathematical models in describing the dose-response relationship (EPA, 1987j). The OAQPS examined a number of health endpoints for ozone. The endpoint which had the greatest data base was pulmonary function. The means of measuring the effect was by forced expiratory volume (FEV) of the lungs during various exposures and exercise levels. The data demonstrated a lowest observed effect level, pulmonary function loss, by decreased FEVs, at .12 ppm ozone. The OAQPS indicated that identifying an adverse

response level from the range of responses to ozone was a topic of debate, and chose to defer the decision.

Unlike the focus in other non-cancer dose-response assessments, the ozone assessment focused on how incidence was affected by dose. Dose and incidence were the variables used in the models for a specific endpoint (e.g. an FEV of 10%). The dose-response relationship is expressed in the model in terms of a conditional probability density (EPA, 1987i).

The assessment does not explicitly consider the concept of a threshold response. Instead, a range of low level responses are identified, and an adverse response (or range of responses) is selected. Very low level responses are ignored by the OAQPS because: 1) responses below background levels (assumed to be in the range of .01 -.015 ppm) are not considered relevant to regulation, and 2) "it is difficult to characterize the very small hypersensitive fraction of the population that might respond at ozone levels below background." (EPA, 1987i; EPA, 1987j).

The data from the models are used to derive probabilistic estimates of risk in the final risk characterization. As a result, the final risk characterization is unique from the straightforward comparison of Rfd to exposure, performed in the risk characterization step of most other programs.

b) Lead

The OAQPS employed a decision-analytic approach to assess the dose-response relationship for lead in developing a NAAQS (Wallsten, 1986). The population of concern in the lead assessment was young children. Data was very incomplete regarding dose-response relationships for lead and young children, which motivated the use of the decision-analytic technique. As with modelling techniques, the use of the decision-analytic technique is expensive and resource intensive.

c) Reasons for OAR Dose-response Assessment Methods

A number of explanations have been offered for the use of the complex dose-response assessment techniques employed by the OAQPS in setting NAAQS. As mentioned earlier the costs of regulation are a likely reason for using the modelling and decision-analytic techniques. Other possible explanations include: the few chemicals required by statute to be regulated under NAAQS permits the use of the time and resource intensive techniques; adequate human data was available for the analysis; the OAQPS simply had a preference for high-tech assessment methods. Each of these explanations is likely, and it is possible that all may have influenced the decision to use the techniques. However, several clarifications are necessary.

The fact that human data was available was a result in part of the OAQPS's decision to focus on short-term

effects, which are reversible. Such focus permitted the ethical collection of the human data. Such human data would not have been available if effects from chronic exposures were assessed. The OAQPS indicates that there was reason to suspect adverse effects from chronic exposure to ozone: "...chronic exposures to ozone may be more serious than acute exposure effects" (EPA, 1987j). The OAQPS failed to consider a chronic standard for ozone, because of the difficulties encountered in extrapolating from animal to human data: "...extrapolation of chronic toxicology results is currently premature" (EPA, 1987j). The Office believed that further evidence was necessary regarding the sensitivity of effect between animals and humans.

By claiming an inability to develop a chronic ozone standard the OAQPS was implicitly denying the value of the Rfd approach. Some data from animal studies was available which allowed for the calculation of an Rfd. The lowest adverse effect level for ozone identified in an animal study appears to have been 0.64 ppm (EPA, 1987j). If the standard Rfd approach is employed, the resulting ozone standard would be .00064 ppm (based on the use of the required 1000 fold uncertainty factor when extrapolating from an animal LOAEL). The problem identified by the OAQPS in using this approach is that the resulting standard is far below background levels of .01 - .015 ppm. A chronic ozone standard based on the Rfd would require the clean-up

of ozone beyond background levels, which would be extremely expensive if even possible.

Of course more studies may produce a more realistic Rfd value (identification of a NOAEL instead of simply a LOAEL). However, the OAQPS doubted that a value derived by the Rfd could produce such a realistic value. The OAQPS thought that the technique of extrapolation from animal to human contexts offered by the RFd approach (i.e. 10 fold uncertainty factor) was too crude for its purposes. The Office is currently seeking better quantification of the uncertainties between animal and human sensitivities, in order to eventually develop a chronic ozone standard.

2) National Emission Standards for Hazardous Pollutants (NESHAPS)

The EPA also promulgates National Emission standards for Hazardous Air Pollutants (NESHAPS) pursuant to section 112. The Act defines a NESHAP as

"...an air pollutant to which no ambient air quality standard is applicable and which in the judgment of the Administrator causes, or contributes to, air pollution which may reasonably be anticipated to result in an increase in serious irreversible, or incapacitating reversible illness."

The purpose of this report is to provide a foundation for an OAR decision regarding how to assess risks from non-cancer health effects in the NESHAP context. Concluding

remarks will recommend a dose-response assessment alternative for the NESHAP program. However, before making this recommendation, alternatives which have already been considered by the OAR are described.

The use of the type of probabilistic risk assessment used in the NAAQS assessments was proposed for the non-cancer NESHAPs (Wallsten, 1987). However, the probabilistic risk assessment in the NESHAP context was considered infeasible because of: 1) expensive and time consuming methodology would be inappropriate for the large number of pollutants which must be reviewed within a short time span; 2) many of the pollutants are found in limited areas around specific stationary sources which restricts available data inputs.

A more economical probabalistic risk assessment approach, which was less information intensive than the approach used in the lead NAAQS assessment, was also proposed (Wallsten, 1987). The OAQPS has decided not to use this modified probabilistic approach because of the expense that would be involved in applying the procedure to the number of pollutants regulated under section 112.[21]

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[21] It is assumed that the expense imposed by controls needed to meet NESHAPs would not be as great as the expense imposed by the NAAQS program. NAAQS pollutants are more widespread than NESHAP pollutants, and therefore require greater regulatory effort. As a result, NESHAPs do not demand the same level of risk quantification as the NAAQS.

III. SUMMARY AND CONCLUSIONS

A review of EPA program office activities indicates that the offices have been regulating chemical substances based on their non-cancer health effects. All of the program offices surveyed (except for the Air and Radiation Office) have been using the Rfd approach to assess risks from these substances. The Rfd (or ADI) approach has been used by a variety of organizations and Agencies prior to its use within the EPA. This precedent appears to have contributed to the widespread use of the approach within the EPA. Despite some criticisms of the Rfd approach (see section II (C) above) there is a tendency to defer to the use of the Rfd approach, and the standard application of uncertainty factors.

An additional reason for the widespread use of the Rfd is a lack of a reasonable alternative. Modelling techniques allow for greater quantification of uncertainties, and are generally sought by Program Offices for use in dose-response assessments. However, such techniques are generally prohibitive for most regulatory use because of excessive resource costs, and gaps in scientific knowledge regarding the mechanism of non-cancer effects.

The use of modelling has been limited to the NAAQS program within the Air Office. The use of the technique in the NAAQS program has been attributed to the need for well substantiated standards, due to the excessive costs imposed

on the regulated community by the standards, and the few chemicals regulated under the program.

IV. RECOMMENDATIONS FOR NESHAP PROGRAM

The NESHAP program needs to come up to speed with Agency efforts to regulate chemical substances based on their non-cancer health effects. Given the demands imposed on the program by the quantity of substances regulated under section 112, the Rfd approach should be utilized for performing the dose-response assessment. The Rfd approach offers an economical and efficient means to assess non-cancer risks under section 112. The widespread use of the Rfd approach and its historical precedence also support the use of the technique in the NESHAP context.

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